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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/473,872	Yoon, K.
Examiner	**Art Unit**
Joseph Woitach	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 6, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *40-42* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *40-42* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 6, 2003, paper number 24, has been entered.

DETAILED ACTION

This application is an original application filed December 28, 1999.

Applicant's amendment filed February 6, 2002, paper number 25, has been received and entered. Claims 1-39 have been canceled. Claim 40 has been amended. Claims 41 and 42 have been added. Claims 40-42 are pending and currently under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 40 rejected under 35 U.S.C. 103(a) as being unpatentable over Yoon *et al.* (PNAS, 1996) and Alexeev *et al.* (Nature Biotech, 1998) in further view of, Uttam *et al.* (PNAS, 1996), Christiano *et al.* (PNAS, 1994) and Cole-Strauss *et al.* (IDS reference; Science, 1996) is withdrawn.

The amendment to claim 40 has differentiated the claimed invention from that taught in the cited references. Specifically, upon review of amended claim 40 and the teachings of the references it is noted that Alexeev *et al.* teaches the same RDO sequences (Tyr-A RNA-DNA) as used in the instant specification to correct the tyrosinase gene and provides teaching that this gene mutation is associated with albinoism, however the experiments are performed with cells *in vitro*

and provide no specific teaching for the recited method step for the delivery to skin cells *in vivo*. Additionally, Yoon *et al.* provides similar experimental evidence *in vitro* for the effectiveness of using an RDO to correct an altered gene and the specific motivation to adapt the use of an RDO in gene therapy protocols, however the reference does not provide the method step for delivery to cells *in vivo*. The teachings of Uttam *et al.*, Christiano *et al.* and Cole-Strauss *et al.* were provided for the teachings of mutations in genes other than the tyrosinase gene and no longer apply to the pending claim. Because the references used in the basis of the rejection fail to teach each limitation set forth in the claim, the rejection is withdrawn.

Claims 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoon *et al.* (PNAS, 1996), Alexeev *et al.* (Nature Biotech, 1998) and Furth *et al.* (US Patent 5,998,382) in further view of Gilchrest *et al.* (US Patent 5,580,547) and Stout *et al.* (US Patent 6,319,224).

Amended claim 40 is directed to a method of correcting a mutation in skin cells *in vivo* comprising delivering the Tyr-A RNA-DNA RDO oligonucleotide to skin cells in an amount effective to cause stable genetic correction of the tyrosinase gene wherein the correction results in tyrosinase enzyme activity. Newly added dependent claims recite two specific routes of delivery, topical application (claim 41) and intradermal injection (claim 42). At the time of filing Alexeev *et al.* teaches the RDO sequence Tyr-A RNA-DNA (see figure 1A) for the correction of the tyrosinase gene. Alexeev *et al.* teaches the RDO sequence Tyr-A RNA-DNA is effective in methods of delivery for altering the tyrosinase gene in primary melanocyte isolated from albino mice. Further, Alexeev *et al.* teaches several different reagents to optimize the delivery of the Tyr-A RNA-DNA to the cells and demonstrates the effective uptake of the oligonucleotide by the cells (page 1344, bridging first and second column and results in figures 2 and 3). Finally, Alexeev *et al.* teaches that this sequence is effective in altering the endogenous tyrosinase gene and that after providing the Tyr-A RNA-DNA the tyrosinase enzyme activity is restored (see summary in abstract and figure 3). Alexeev *et al.* teaches that other RDO sequences have been used effectively *in vitro* and *in vivo* in methods to provide stable genetic changes in a gene of interest (page 1343, first column indicating the teachings of references 1-4, 10 and 11). For example, Yoon *et al.* (cited by Alexeev *et al.* as reference 1) teaches methods of

using a chimeric RNA-DNA oligonucleotide to target disease related mutations. In particular, Yoon *et al.* teach that the methods disclosed demonstrate the feasibility of using chimeric RNA-DNA oligonucleotides in gene therapy protocols and specifically indicate that experimental results should be extended to therapeutic strategies in treating human diseases (page 2071, second column and page 2076, first column final paragraph). Like Alexeev *et al.* Yoon *et al.* provides the specific methodology and motivation for the delivery of a chimeric RNA-DNA oligonucleotide to a primary cell to correct a genetic disorder, however Yoon *et al.* fails to provide the specific methodology for affecting *in vivo* delivery. At the time of filing, various methods for the delivery of a polynucleotide to the skin were known. For example, in summarizing what was known in the art Furth *et al.* teach that polynucleotides can be delivered to the skin by (a & b) smearing of the polynucleotide onto an affected portion of the skin (topical application-claim 41), (c) intradermal inoculation (claim 42) and (d) interdermal inoculation (column 1, lines 37-45). Similarly, Stout *et al.* teach that various routes for delivery of a polynucleotide were known (column 1, lines 25-35), and specifically teach a method and device for the intradermal delivery to the skin by injecting a polynucleotide based medication into a subject (see figure 3 and 4 for device and column 2, lines 35-49). Gilchrest *et al.* teach and review specific methods for the topical application and delivery of polynucleotides to the skin to affect skin pigmentation (bridging columns 2-3). In summary, at the time of filing various methods for the delivery of a polynucleotide to the skin were known, and very specific methodology and devices had been developed to provide a polynucleotide to the skin of a

subject. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the specific methodology known in the art for the delivery of a polynucleotide to the skin of a subject as taught by Furth *et al.*, Gilchrest *et al.* and Stout *et al.* for the delivery of the TyrA RNA-DNA to correct the tyrosinase gene as taught by Alexeev *et al.* Both Alexeev *et al.* and Yoon *et al.* specifically teach that chimeric RNA-DNA polynucleotides can be used for correcting gene mutations, and Yoon *et al.* specifically teaches that chimeric RNA-DNA polynucleotides should be adapted from the experimental models to protocols of gene therapy. Therefore, given the success of the methods for correcting the tyrosinase gene in primary skin cells through the use of the TyrA RNA-DNA polynucleotide as demonstrated by Alexeev *et al.*, and the specific teaching of Yoon *et al.* to use RNA-DNA polynucleotides in gene therapy protocols, one having ordinary skill in the art would have been motivated to use the specific methodology for the delivery of a polynucleotide to a skin cell known in the art as taught and exemplified by the teachings of Furth *et al.*, Gilchrest *et al.* and Stout *et al.* Alexeev *et al.* demonstrate the ability of the TyrA RNA-DNA polynucleotide to affect a genetic change in the tyrosinase gene in primary cells, therefore there would have been a reasonable expectation of success to practice the claimed method for correcting a mutation in the tyrosinase gene because both the methods of delivery and the method of affecting the tyrosinase gene were demonstrated to be effective at the time of filing.

To the extent that Applicants' arguments apply to the instant rejection, applicants note that the specification provides specific teaching regarding the unexpected results of practicing the

claimed method. In particular, Applicants point to pages 15 and 38 which indicate that topical and intradermal delivery of the TyrA RNA-DNA polynucleotide resulted in "[s]urprisingly, a high level of gene correction approaching 40%" (see specification page 38 and page 3, second paragraph of Applicants' amendment). Furthermore, it is argued that the specification, not the claims, should contain the unexpected results of the claimed invention and may be relied upon for rebutting a prima facie case of obviousness citing *In re Soni, In re Chupp* and *In re Albrecht* in support of their arguments. Applicants argue that the showing of the advantage of the claimed invention in the instant specification is sufficient and is commensurate in scope with the present claims. See Applicant's amendment, pages 3-4. Applicant's arguments have been fully considered.

First, it is noted that Alexeev *et al.* teach the same TyrA RNA-DNA polynucleotide used in the instant specification and instantly claimed. Since the polynucleotide disclosed in the present specification is the same as that disclosed in the art, any method using the TyrA RNA-DNA polynucleotide would result in the same outcome. To the argument to whether the use of the TyrA RNA-DNA constitutes an unexpected result the courts have stated that reliance upon inherency is not improper even though rejection is based on Section 103 instead of Section 102. *In re Skoner*, et al. 186 USPQ 80 (CCPA). In the instant case, since the RNA-DNA polynucleotide in the art and that being claimed are the same, any result or outcome of using the RNA-DNA polynucleotide would be the same and would not represent an unexpected result. In contrast to the findings in *In re Chupp*, because the TyrA RNA-DNA disclosed in the art and

taught in the specification are the same, the *Papesch* doctrine applied in *Chupp* would not apply because the rejection does not rely on structural similarities rather the product in use is the same (*ibid.* page 1439), and thus, the unobvious or unexpected advantageous properties are provided in the product disclosed in the art. Similarly, in *In re Albrecht* the courts applied the decision of *In re Papesch* and stated that "Our position is that from the standpoint of patent law a compound and all of its properties are inseparable" (page 589). Therefore, since the TyrA RNA-DNA disclosed in the specification and the prior art is the same, any property or affect of using the product would be expected.

With respect to the methodology for delivery providing the unexpected result, it is noted that claim 40 is broad encompassing any method of delivery to a skin cell, and on its face is not commensurate in scope with the intradermal and topical methods of delivery taught in the present specification. As discussed in *In re Soni* the unexpected results must be commensurate in scope with the claims. Additionally, the courts have stated that "The evidence presented to rebut a *prima facie* case of obviousness must be commensurate in scope with the claims to which it pertains." (*In re Dill*, 604 F.2d 1356, 1361, 202 USPQ 805, 808 (CCPA 1979)). Here, claim 40 is very broad encompassing any method of delivery and does not recite the specific parameters used to obtain the result indicated as 'surprising'. Thus, with regard to the unexpected results Applicant argues are disclosed in the present specification, Applicant's arguments are not persuasive because the methods encompassed by claim 40 are not specifically drawn to the unexpected result pointed to by Applicant. With respect to newly added claims 41 and 42, it is

noted that these claims are restricted to the specific means of delivery pointed to by Applicant for providing the surprising 40% of cells assayed being transformed. Initially, beyond the mere statement that the surprising affect was observed, the specific affect can not be fully appraised or evaluated based on the evidence of record, because the number of cells or area assayed is not clearly set forth. Clearly the teaching of Alexeev *et al.* provide that primary melanocyte cells can be affected, and that they are not recalcitrant to the affects of the TyrA RNA-DNA polynucleotide administered. Similar to claim 40, dependent claims 41 and 42 are broad encompassing any means of topical or intradermal delivery (i.e. delivery of the RNA-DNA by itself, in any type of liposome or delivery vehicle or by any device intradermally, and in both cases in any effective amount), and based on the guidance and evidence of record the specific scope which provide the surprising result can not adequately be determined with respect to delivery method. Furthermore, the stated surprising result of 40% in the specification is meaningless because the specific methods which led to this result are not clearly set forth, nor is there is a context in which the percentage of cells was determined. Accordingly, since the claimed methods for the delivery of a polynucleotide, either topically or intradermally, were known at the time of filing, and the present claims generically encompass any of these means known in the art, it is found that claims 41 and 42 are not commensurate in scope with what the specification states are surprising results. Additionally, as discussed above, because the TyrA RNA-DNA delivered is the same as that disclosed in the prior art the use of any of the delivery methods known in the art would result in the same outcome. The claimed methods as claimed

are obvious over the teachings of Yoon *et al.*, Alexeev *et al.*, Furth *et al.* Gilchrest *et al.* and Stout *et al.* Applicant's arguments that the claimed method is unobvious because of unexpected results which do not have to be recited in the claim are not persuasive because the pending claims are broader than the specific method disclosed and used which provided the surprising result.

Finally, examiner notes that upon review of the specification it appears that it is neither the specific TyrA- RNA-DNA polynucleotide nor the delivery method that provides for affecting 40% of cells assayed. Rather, it appears that the assay which determined up to 40% of cells being tested were still transformed was performed at a time much later than the initial administration step and possibly after the expected life span of a terminally differentiated primary melanocyte. It appears that what may have been considered surprising to Applicant was that a non-terminally differentiated cell or a cell which was less differentiated was affected by the methods. Thus, affecting a non-terminally differentiated cell or a skin stem cell would allow for the genetic alteration generated to be observed in more cells than cells initially treated because the non-differentiated cells would be capable of proliferating and dividing. However, as discussed above, the specification fails to provide a clear and adequate description of the specific experiments performed or relied upon in Applicants arguments.

Thus, the claimed invention, as a whole was *prima facie* obvious absent to the evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 40-42 are provisionally rejected under the judicially created doctrine of double patenting over claims 1, 2, 8, 16-18 of copending Application No. 09/962,628. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, *e.g.*, *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to isolating and/or maintaining mammalian and murine embryonic stem cells including mouse embryonic stem (ES) cells (see for example dependent claims 33 and 43) whereas the claims of US Patent 5,166,065 are drawn to isolating and maintaining mouse embryonic stem cells. Both methods comprise the same essential steps wherein said ES cells are cultured in media comprising an effective amount of recombinant leukemia inhibitory factor (LIF) under sufficient conditions. Further, dependent claims in the instant application and the '065 patent each set forth the same specific ranges for the concentration of LIF to be added to the culture media. Claims 31-66

cannot be considered patentably distinct over claims 1-16 of '065 because the practice of the methods in a mouse, a mammal and a murine species, would anticipate instantly claimed methods set forth in claims 31-66.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

US Patent 5,760,012 (Kmiec *et al.*) teach methods of making and using chimeric repair vectors (CRV) which are equivalent to the RNA-DNA oligonucleotides (RDO) taught in the instant application. Kmiec *et al.* teach that a CRV/RDO can be used to treat diseases caused by mutations focusing on diseases associated with blood. In particular, the methods focus on diseases associated with the blood because the methods taught require removal, treatment and readministration of a cell from a subject. The methods of Kmiec *et al.* differ from those instantly disclosed because the cell is removed wherein the treatment of the skin the cell to be treated is affected is *in vivo*. However, the teaching of Kmiec *et al.* demonstrate the feasibility of using CRV/RDO technology to correct diseases and disorders associated with genetic mutations.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach